

# THE SIGNIFICANCE OF ADVENTITIAL INFILTRATIONS IN CORONARY ATHEROSCLEROSIS

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There are a large number of deaths from coronary disease in which a necropsy examination generally gives less evidence of the exact cause of death than the clinical findings. In the absence of fatal structural lesions, acute coronary deaths have been attributed to disturbances of function such as inhibition, arrhythmias, and coronary spasm; but the problem has been one of debate rather than observation. Albutt rejected the spasm theory in no uncertain terms, saying "The truth is, spasm of the coronary arteries is a nosologist's conceit to explain puzzles of his own making."

The object of this investigation was to attempt to establish some correlation between the histological features of the coronary arteries and the mode of dying. Attention was directed to the changes in the adventitia and in particular to the frequent occurrence therein of discrete foci of inflammatory cells. The incidence of these lesions is analysed, the appearances described, and their significance discussed.

## METHOD

The observations presented here are based on the histological examination of the coronary arteries obtained from 160 necropsies. Of these, 101 were from cases dying of coronary artery disease, and 59 from cases in which death was due to some other cause. These are hereafter referred to as "coronary cases" and "non-coronary cases."

The coronary cases were classified independently of the histological findings into three groups. Group I: sudden deaths with coronary atherosclerosis, but no macroscopic evidence of thrombosis or myocardial infarction or fibrosis. Group II: sudden deaths with old infarction or myocardial fibrosis. Group III: deaths due to recent myocardial infarctions.

To some extent this may be considered as a classification of the immediate cause of death. In Group I the immediate cause of death was a functional disturbance rather than an anatomical lesion. In Group II, anatomical lesions were present and may be implicated, although, as these were old lesions, their presence may not always have had direct bearing on the mode of death. In Group III the anatomical lesions were more recent and may reasonably be considered to have had a more direct relationship to the immediate cause of death, although a terminal functional disturbance could not be excluded.

In all cases the histological appearances were graded according both to the degree of atheroma and to the degree of focal adventitial infiltration.

The degree of atheroma was arbitrarily assessed according to the degree of the narrowing of the lumen, and divided into four grades. Grade O: no atheroma. Grade I: slight atheroma with insignificant narrowing of the lumen. Grade II: moderate narrowing of the lumen. Grade III: complete or almost complete occlusion.

The adventitial changes were classified into four grades. Grade O: no adventitial infiltration (negative). Grade I: a scanty incidence of small or early focal infiltrations. Grade II: a small or moderate number of well-formed foci. Grade III: many well-formed foci. Grades I, II, and III are collectively referred to as "positive."

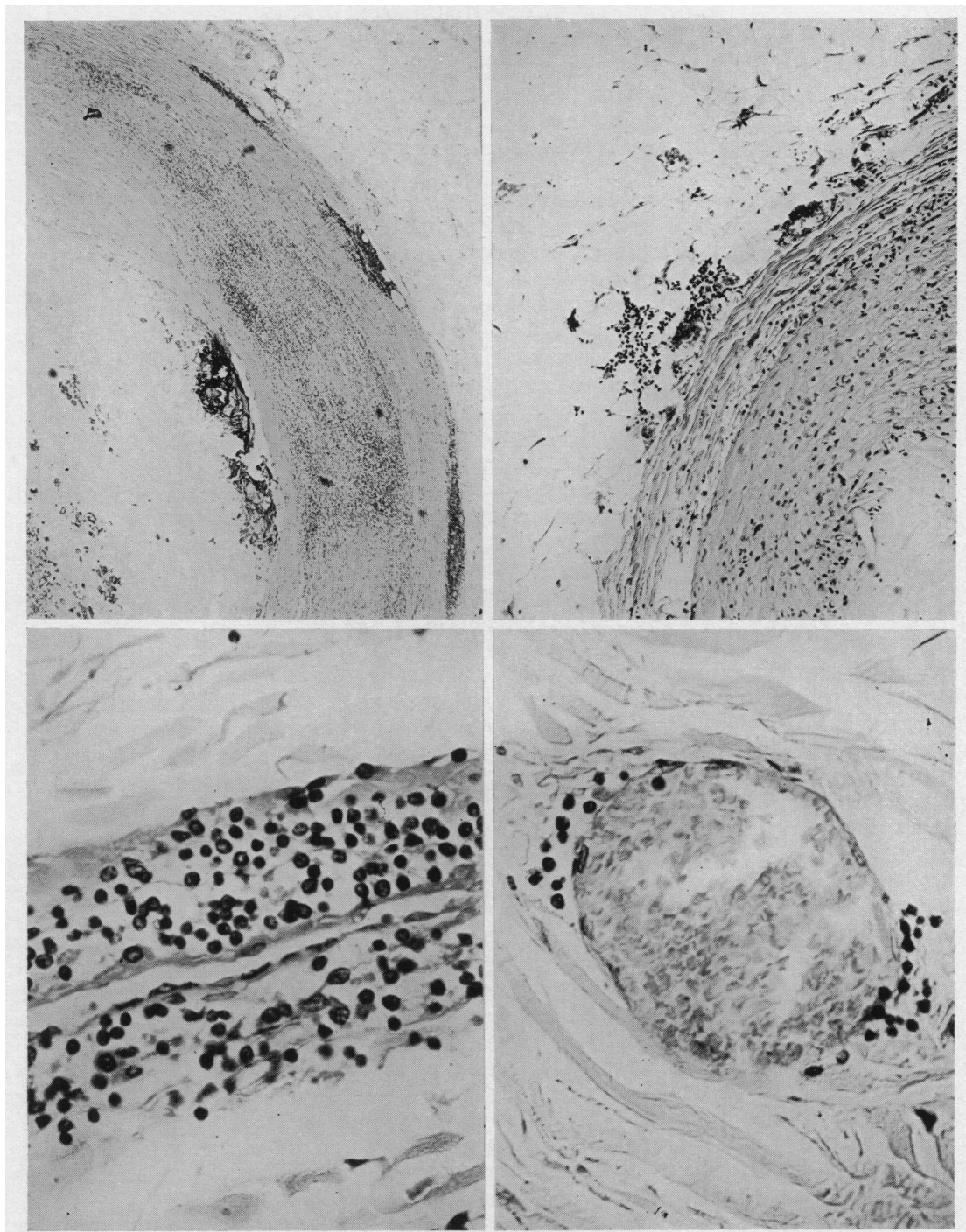


FIG. 1.—(A) Low-power view of a segment of an atheromatous coronary artery showing three foci of infiltration in the outer zone of the adventitia. (B) A small irregular focus of cellular infiltration at the periphery of the adventitia abutting directly onto the epicardial fat. (C) High-power view of an adventitial focus surrounding a small capillary in longitudinal section. The uniform cell type is demonstrated. (D) An early perivascular lesion of bipolar type in association with a dilated adventitial capillary.

## THE ADVENTITIAL LESIONS

Adventitial changes receive scanty recognition in studies of coronary atherosclerosis. This is probably due to the fact that atheroma is primarily a disease of the inner coats of the artery, and studies directed to the pathogenesis of the disease tend to focus on the intimal and medial lesions. The present series of observations is in no way concerned with the ætiology of the atheromatous disease, but attempts to throw some light on the mechanism by which such lesions may cause sudden death.

Gould (1953) mentions the occurrence of adventitial infiltrations in coronary atheroma and passing reference is made to it in cases reported by Miller and Woods (1943) and Zachs (1943). The presence of adventitial infiltrations in acute fatal coronary occlusions in young soldiers has been noted by Reich (1948), Saphir and Gore (1950), French and Dock (1944) and Yater *et al.* (1948). Saphir and Gore suggested that they may represent a primary inflammatory process to which the intimal changes are secondary, producing, in later stages, an appearance that cannot be distinguished from, or is identical with arteriosclerosis. Horn and Finklestein (1940), in a study of 100 fatal cases of coronary occlusion, recognized adventitial infiltration as a frequent accompaniment of coronary arteriosclerosis and draw attention to the possibility of confusion with syphilitic disease. Hausemann (1949) regarded this cellular infiltration, which he found in nearly all cases of coronary atherosclerosis, as the expression of a secondary reparative process.

The adventitial lesions consist of discrete foci of small round cells which appear to be identical with lymphocytes (Fig. 1). The distribution is essentially perivascular, forming collars around the vasa vasorum of the large coronary arteries. Early lesions can be identified as small groups of cells immediately adjacent to the vasa, and the typical established foci are of elliptical or crescentic shape when seen in transverse section. In some cases the foci are confluent producing an encircling zone around the coronary artery. These foci were not observed in association with smaller intramuscular vessels in the myocardium.

The cellular exudate or infiltrate appears to be of a pure or unicellular type (Fig. 1C), in contrast to the pleomorphic nature of the infiltrations sometimes seen in the medial layer in an area of degenerate atheroma, where plasma cells, granulocytes, macrophages, and even fibroblasts may be present. It also bears no similarity to the diffuse infiltrations as seen in polyarteritis nodosa, where eosinophil granulocytes form a prominent part of the picture, or to the histological appearances of mycotic arteritis.

In a small proportion of lesions the foci of infiltration were related to a nerve rather than to a vessel. In such cases the primary relationship is probably with the perineural lymphatics as the infiltration was entirely outside the nerve sheaths and there was no evidence of pathological change in the nerve fibres themselves.

The site of the foci appears to be determined by the position of the vasa vasorum. If these are situated in the inner portion of the adventitia, the foci may appear to be surrounded by connective tissue, and if this shows excessive fibrosis the resulting appearance may be suggestive of fibrosis directly associated with the focus. Further observation, however, shows no relationship between the degree of adventitial fibrosis and the existence or distribution of these foci.

When the vasa vasorum are situated in the outer zone of the adventitia, the foci present tend to be superficial and abut directly onto normal epicardial fat. In some instances lesions could be seen at some distance from the artery, as isolated groups of small round cells lying in the adipose tissue, in association with a capillary blood vessel, with no suggestion of cell damage or fibrosis.

*Incidence of Adventitial Foci.* Details of the incidence of adventitial infiltrations in the coronary and non-coronary cases are shown in Table I and Fig. 2.

Of the 101 coronary cases 80 per cent showed adventitial infiltrations, whereas these were present in only 29 per cent of the 59 control cases. This difference is in itself of high statistical significance even though many of the controls were selected as potential "positives," after preliminary observations had indicated that certain types of non-coronary deaths appeared to be associated with the incidence of the adventitial foci.

TABLE I  
DISTRIBUTION OF 160 CASES CLASSIFIED BY "MODE OF DEATH" AND DEGREE OF ADVENTITIAL INFILTRATION

Degree of infiltration	Coronary deaths						Non-coronary deaths	
	Group I		Group II		Group III			
	Cases	%	Cases	%	Cases	%	Cases	%
O	4	8.5	9	26.5	7	35	42	71.0
I	23	49	17	50	6	30	11	18.7
II	17	36	6	17.5	6	30	5	8.6
III	3	6.5	2	6	1	5	1	1.7
Total ..	47		34		20		59	

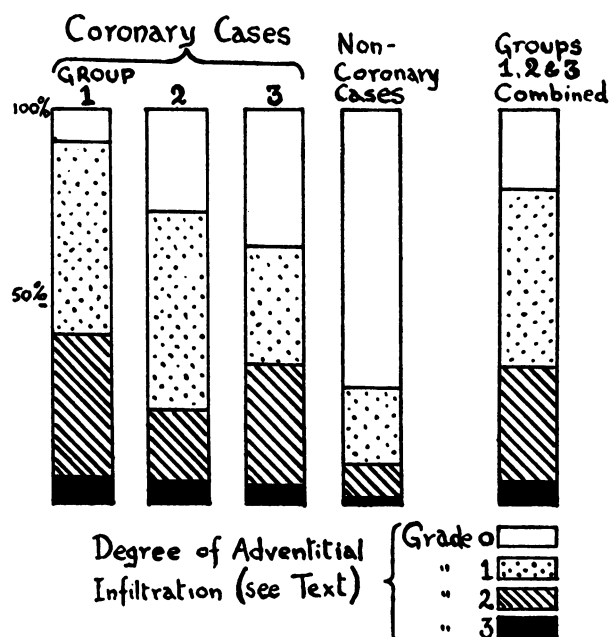


FIG. 2.—Percentage incidence of adventitial infiltration.

Separation of the coronary cases into groups as previously described, showed a significant difference in the incidence of infiltrations. In Group I (acute coronary deaths without infarction), 44 of 47 cases showed infiltrations, i.e. over 90 per cent positive. In Groups II and III respectively, 25 of 34 cases, and 13 of 20 cases were positive (74 and 65%). This difference between Groups II and III is not significant.

No significant relationship was established between the degree of coronary atheroma and the incidence of adventitial infiltrations. In Table II the distribution of atheroma grades in those cases showing infiltrations are compared. The non-coronary positives show a significantly lower degree of atheroma than the coronary positives. No correlation was found with sex or age distribution, adventitial infiltrations being found in subjects between 33 and 91 years of age.

TABLE II  
ATHEROMA INCIDENCE IN "CORONARY" AND "NON-CORONARY" CASES SHOWING ADVENTITIAL INFILTRATIONS

Atheroma grade	Coronary		Non-coronary	
	Cases	%	Cases	%
1	4	5	5	29
2	32	39	8	47
3	45	56	4	24

The inferences drawn from the statistical analysis are that the adventitial infiltrations are not related to the degree of coronary atheroma but rather to the mode of dying.

If the atheroma itself is not responsible for the infiltrations some useful information on the aetiology of these adventitial lesions might be obtained by reference to the modes of death in the non-coronary cases in which such lesions occurred. Could some common denominator be found in these cases that had died of diverse causes, and if so could this same factor be held to be responsible to some extent, for the fatal outcome of the cardiac disease in the coronary group?

Of the 59 non-coronary cases 17 showed the presence of adventitial infiltrations and in each of these cases an anoxic element was associated with the mode of death. Infiltrations were present in three of the six cases of carbon monoxide poisoning, and three of the five cases of hanging and strangulation. Of the 19 cases of intracranial lesions eight were positive, the majority being cases of massive cerebral hæmorrhage. The anoxic element in fatal coma associated with cerebral hæmorrhage is well recognized clinically, and it is suggested that the high incidence of infiltrations in the adventitia of the coronary arteries in such cases (six out of ten) is a reflection of the respiratory insufficiency. By contrast none of the six cases of subarachnoid hæmorrhage showed infiltrations. It is considered that this apparent discrepancy is explained by the difference in duration of the terminal coma, which in the cerebral hæmorrhage cases was invariably a matter of several hours, whereas in the subarachnoid hæmorrhage cases death generally occurred in a matter of minutes. In one case a large area of cerebral softening and œdema produced a similar clinical picture to that of a cerebral hæmorrhage and this too was "positive." One patient died of broncho-pneumonia after several hours of progressive cyanosis and respiratory distress. This case was "positive." The other two (negative) cases of pneumonia were clinically toxæmic deaths.

Of the hæmorrhagic cases two of the five were "positive" the remaining negative ones died almost instantaneously following massive hæmorrhages.

The lesions in a patient who died of respiratory failure due to acute bulbar poliomyelitis were classified as negative as no focal infiltrations were present in the coronary adventitia, but there was in fact an atypical diffuse adventitial infiltration.

#### DISCUSSION

It is suggested that focal adventitial infiltrations in the coronary arteries of the non-coronary cases are associated with, and in fact caused by, a state of anoxia. This hypothesis is supported by the findings of Gruenwald (1949) who reported changes in the coronary arteries, including adventitia infiltrations, in 21 stillborn or newborn infants, all of whom showed varying degrees of asphyxia.

If anoxia is considered responsible for adventitial infiltrations in these non-coronary deaths, it can reasonably be assumed to play a local role in the coronary group, as it was only in the coronary deaths that these adventitial lesions were found in the absence of generalized anoxia.

Examination of the incidence and microscopic appearances of the adventitial foci does not support suggestions that they are essentially a part of the atheromatous process in itself or that they are due to local inflammation or toxæmia. The dissociation of the incidence of infiltrations with that of atheroma has already been remarked upon, and one does not find such adventitial lesions in atheromatous areas of the aorta or limb arteries.

It is suggested that local anoxia occurs in the fatal coronary cases as a result of spasm of the vessels, particularly the small vessels of the coronary adventitia. Specific localization in the heart can only be partly explained by suggesting a disproportionate degree of anoxia due to the high oxygen requirement of the heart muscle, as infiltrations are not found where the oxygen tension might be assumed to be lowest, that is, in association with the small intramyocardial branches of the coronary arteries. This suggests that the local perivascular anoxia is associated with an active participation of the vessels concerned, namely spasm.

The micro-anatomical relationships of the adventitial foci to the coronary arteries do not support the view that the infiltrations are part of the atheromatous process. The foci are often found at sites corresponding to the lesser degree of atheroma in a particular vessel, and are often quite isolated from the artery itself. Even when quite large, the lesions do not display any signs of organization or fibrosis which suggests that they are related to the terminal mechanism responsible for death.

The hypothesis that infection might be the cause of the infiltrations does not stand up to close examination. No doubt mycotic infection of coronary arteries can, and does occur, but it is considered very improbable that such a factor was present in the lesions in 80 per cent of the present series of 101 cases of acute coronary deaths. On similar grounds, the views that generalized primary inflammation (Saphir and Gore, 1950) or intoxication (Nelson, 1941) may be responsible for the lesions, appear to be untenable and also they fail to explain the localization to the coronary vasa vasorum, whereas polyarteritis nodosa shows no such localization.

Karsner and Bayless (1934) described changes in the coronary arteries in association with rheumatic carditis. The histological appearances, however, differed from those of the adventitial lesions described in this paper, and in the two cases in the present series in which there was a clinical history or pathological evidence of previous rheumatic carditis no adventitial infiltrations were found.

Albertini (1943) has described a condition in young adults which he called "Arteritis chronica stenosans coronariæ" and this has been further described by Walthard (1942): perivascular and perineural infiltrations were found which appeared to be similar to those described in the present series. These authors considered that the lesions were not atheromatous, but were due to a meta-static mycotic arteritis due to focal infection, and that the pathological process was initially an adventitial change which spread to the media and intima. It is improbable that this explanation holds true for the findings in the present series and it is disputed whether this arteritis chronica stenosans coronariæ is indeed a specific entity. That spasm, rather than anatomical change, is responsible for many of the clinical symptoms of coronary insufficiency is demonstrated by the symptomatic relief in cases of angina, on administration of vasodilator substances such as nitrites. Interference with the sympathetic nerve pathways by ganglionectomy also improves the prognosis in experimental coronary occlusion in animals (Cox *et al.*, 1936, and Shauer *et al.*, 1937). The association of the adventitial infiltrations with the vasa vasorum of the larger coronary arteries and not with the smaller branches is in agreement with Woollard's (1926) findings that the larger coronary arteries are predominantly innervated by branches of the sympathetic nerve whereas the smaller branches are mainly supplied by the vagus.

Green (1935) showed that profound stimuli from many parts of the body can cause reflex constriction of the coronary arteries which may reasonably be assumed to be possible even in the painless and silent cases of coronary occlusion and myocardial infarction, by means of local ganglion reflexes or even axon reflexes.

In fatal cases, the majority of which may show no significant organic lesion, it is suggested that intense spasm of the vasa vasorum of the coronary arteries causes local anoxia in the adventitia and that this latter state may be recognized by lymphocytic infiltrations. The exact mode of formation of these infiltrations or the time required for their formation is not known, but the cells appear to be of intravascular origin and it is probable that their appearance is preceded by yielding of the vascular spasm to paralytic dilatation. If this is correct it would appear that many of the apparently

sudden or instantaneous cardiac deaths are really the terminal phases of silent "anginal attacks" which may have been present for a considerable time, possibly several hours.

Should this hypothesis, of the dominant role of spasm in the fatal outcome of coronary disease receive confirmation, it might be of advantage to review the methods of treatment of acute coronary insufficiency, particularly in regard to the drugs that depress ganglionic activity.

#### SUMMARY

The incidence of focal adventitial infiltrations in coronary arteries and its relationship to the degree of atheroma and mode of death, in 160 cases, are discussed.

These lesions are considered to be caused by local anoxia as a result of reflex vascular spasm.

It is considered that in the absence of a state of generalized anoxia these infiltrations may be regarded as an indication that coronary artery disease was directly associated with the cause of death and not merely an incidental condition.

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